

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 31/00	A2	(11) International Publication Number: WO 00/23059 (43) International Publication Date: 27 April 2000 (27.04.00)
(21) International Application Number: PCT/US99/23769 (22) International Filing Date: 18 October 1999 (18.10.99) (30) Priority Data: 60/104,887 20 October 1998 (20.10.98) US (71) Applicant: ORTHO-MCNEIL PHARMACEUTICAL, INC. [US/US]; U.S. Route #202, P.O. Box 300, Raritan, NJ 08869-0602 (US). (72) Inventors: GORDEY, Marina; 1749 Butler Avenue #8, Los Angeles, CA 90025 (US). OLSEN, Richard; 16816 Mar- quez Avenue, Pacific Palisades, CA 90272 (US). SHANK, Richard; 551 Village Circle, Blue Bell, PA 19422 (US).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: ANTICONVULSANT DERIVATIVES USEFUL IN TREATING ALCOHOL DEPENDENCY, ADDICTION AND ABUSE (57) Abstract <p>Anticonvulsant derivatives useful in treating alcohol dependency, addiction and abuse are disclosed.</p> <p style="text-align: center;"><i>102 and 103 page 6</i></p>		

FOR THE PURPOSES OF INFORMATION ONLY

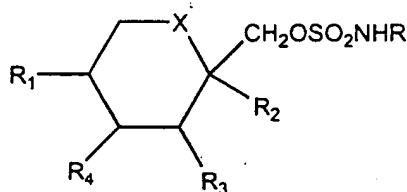
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AI.	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

ANTICONVULSANT DERIVATIVES USEFUL IN TREATING ALCOHOL DEPENDENCY, ADDICTION AND ABUSE

BACKGROUND OF THE INVENTION

Compounds of Formula I:



are structurally novel antiepileptic compounds that are highly effective anticonvulsants in animal tests (Maryanoff, B.E, Nortey, S.O., Gardocki, J.F., Shank, R.P. and Dodgson, S.P. *J. Med. Chem.* **30**, 880-887, 1987; Maryanoff, B.E., Costanzo, M.J., Shank, R.P., Schupsky, J.J., Ortegon, M.E., and Vaught J.L. *Bioorganic & Medicinal Chemistry Letters* **3**, 2653-2656, 1993). These compounds are covered by US Patent No.4,513,006. One of these compounds 2,3:4,5-bis-O-(1-methylethylidene)- β -D-fructopyranose sulfamate known as topiramate has been demonstrated in clinical trials of human epilepsy to be effective as adjunctive therapy or as monotherapy in treating simple and complex partial seizures and secondarily generalized seizures (E. FAUGHT, B.J. WILDER, R.E. RAMSEY, R.A. REIFE, L D. KRAMER, G.W. PLEDGER, R.M. KARIM et. al., *Epilepsia* **36 (S4)** 33, 1995; S.K. SACHDEO, R.C. SACHDEO, R.A. REIFE, P. LIM and G. PLEDGER, *Epilepsia* **36 (S4)** 33, 1995), and is currently marketed for the treatment of simple and complex partial seizure epilepsy with or without secondary generalized seizures in approximately twenty countries including the United States, and applications for regulatory approval are presently pending in several additional countries throughout the world.

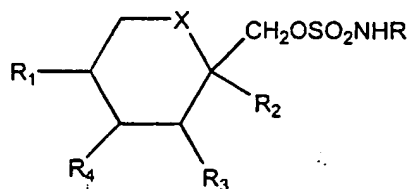
Compounds of Formula I were initially found to possess anticonvulsant activity in the traditional maximal electroshock seizure (MES) test in mice (SHANK, R.P., GARDOCKI, J.F., VAUGHT, J.L., DAVIS, C.B., SCHUPSKY, J.J., RAFFA, R.B., DODGSON, S.J., NORTEY, S.O., and MARYANOFF, B.E., *Epilepsia* **35** 450-460, 1994). Subsequent studies revealed that Compounds of Formula I were also highly effective in the MES test in rats. More recently topiramate was found to effectively block seizures in several rodent models of epilepsy (J. NAKAMURA, S. TAMURA,

T. KANDA, A. ISHII, K. ISHIHARA, T. SERIKAWA, J. YAMADA, and M. SASA, Eur. J. Pharmacol. 254 83-89, 1994), and in an animal model of kindled epilepsy (A. WAUQUIER and S. ZHOU, Epilepsy Res. 24, 73-77, 1996).

Preclinical studies on topiramate have revealed previously unrecognized pharmacological properties which suggest that topiramate will be effective in treating alcohol addiction and abuse.

DISCLOSURE OF THE INVENTION

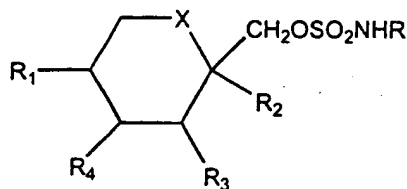
Accordingly, it has been found that compounds of the following formula I:



wherein X is O or CH₂, and R₁, R₂, R₃, R₄ and R₅ are as defined hereinafter are useful in treating alcohol addiction and abuse.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIEMENTS

The sulfamates of the invention are of the following formula (I):

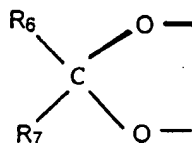


wherein

X is CH₂ or oxygen;

R₁ is hydrogen or alkyl; and

R₂, R₃, R₄ and R₅ are independently hydrogen or lower alkyl and, when X is CH₂, R₄ and R₅ may be alkene groups joined to form a benzene ring and, when X is oxygen, R₂ and R₃ and/or R₄ and R₅ together may be a methylenedioxy group of the following formula (II):



wherein

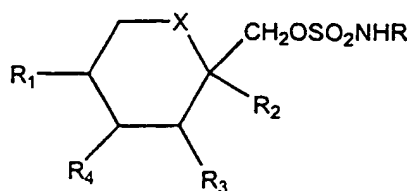
R₆ and R₇ are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

R₁ in particular is hydrogen or alkyl of about 1 to 4 carbons, such as methyl, ethyl and iso-propyl. Alkyl throughout this specification includes straight and branched chain alkyl. Alkyl groups for R₂, R₃, R₄, R₅, R₆ and R₇ are of about 1 to 3 carbons and include methyl, ethyl, iso-propyl and n-propyl. When X is CH₂, R₄ and R₅ may combine to form a benzene ring fused to the 6-membered X-containing ring, i.e., R₄ and R₅ are defined by the alkatrienyl group =C-CH=CH-CH=.

A particular group of compounds of formula (I) is that wherein X is oxygen and both R₂ and R₃ and R₄ and R₅ together are methylenedioxy groups of the formula (II), wherein R₆ and R₇ are both hydrogen both alkyl or combine to form a spiro cyclopentyl or cyclohexyl ring, in particular where R₆ and R₇ are both alkyl such as methyl. A second group of compounds is that wherein X is CH₂ and R₄ and R₅ are joined to form a benzene ring. A third group of compounds of formula (I) is that wherein both R₂ and R₃ are hydrogen.

The compounds of formula (I) may be synthesized by the following methods:

(a) Reaction of an alcohol of the formula RCH₂OH with a chlorosulfamate of the formula ClSO₂NH₂ or ClSO₂NHR₁ in the presence of a base such as potassium *n*-butoxide or sodium hydride at a temperature of about -20° to 25° C and in a solvent such as toluene, THF or dimethylformamide wherein R is a moiety of the following formula (III):



(b) Reaction of an alcohol of the formula RCH_2OH with sulfurylchloride of the formula SO_2Cl_2 in the presence of a base such as triethylamine or pyridine at a temperature of about -40° to 25° C in a solvent such as diethyl ether or methylene chloride to produce a chlorosulfate of the formula RCH_2OSO_2Cl .

The chlorosulfate of the formula RCH_2OSO_2Cl may then be reacted with an amine of the formula R_1NH_2 at a temperature of about 40° to 25° C in a solvent such as methylene chloride or acetonitrile to produce a compound of formula (I). The reaction conditions for (b) are also described by T. Tsuchiya et al. in Tet. Letters, No. 36, p. 3365 to 3368 (1978).

(c) Reaction of the chlorosulfate RCH_2OSO_2Cl with a metal azide such as sodium azide in a solvent such as methylene chloride or acetonitrile yields an azidosulfate of the formula $RCH_2OSO_2N_3$ as described by M. Hedayatullah in Tet. Lett. p. 2455-2458 (1975). The azidosulfate is then reduced to a compound of formula (I) wherein R_1 is hydrogen by catalytic hydrogenation, e.g. with a noble metal and H_2 or by heating with copper metal in a solvent such as methanol.

The starting materials of the formula RCH_2OH may be obtained commercially or as known in the art. For example, starting materials of the formula RCH_2OH wherein both R_2 and R_3 and R_4 and R_5 are identical and are of the formula (II) may be obtained by the method of R. F. Brady in Carbohydrate Research, Vol. 14, p. 35 to 40 (1970) or by reaction of the trimethylsilyl enol ether of a R_6COR_7 ketone or aldehyde with fructose at a temperature of about 25° C, in a solvent such a halocarbon, e.g. methylene chloride in the presence of a protic acid such as hydrochloric acid or a Lewis Acid such as zinc chloride. The trimethylsilyl enol ether reaction is described by G. L. Larson et al in J. Org. Chem. Volaa 38, No. 22, p. 3935 (1973).

Further, carboxylic acids and aldehydes of the formulae $RCOOH$ and $RCHO$ may be reduced to compounds of the formula RCH_2OH by standard reduction techniques, e.g. reaction with lithium aluminum hydride, sodium borohydride or borane-THF complex

in an inert solvent such as diglyme, THF or toluene at a temperature of about 0° to 100° C, e.g. as described by H.O. House in "Modern Synthetic Reactions", 2nd Ed., pages 45 to 144 (1972).

The compounds of formula I: may also be made by the process disclosed in 5,387,700, which is incorporated by reference herein.

The compounds of formula I include the various individual isomers as well as the racemates thereof, e.g., the various alpha and beta attachments, i.e., below and above the plane of the drawing, of R₂, R₃, R₄ and R₅ on the 6-membered ring. Preferably, the oxygens of the methylenedioxy group (II) are attached on the same side of the 6-membered ring.

The activity of the compounds of formula I in treating alcohol dependency, addiction and abuse was evidenced in experimental research studies using a rat model of chronic intermittent ethanol (CIE) ingestion to induce alcohol withdrawal signs. Withdrawal from abused substances like ethanol is typified experimentally in rodents by anxiety, aggressive behavior, hyperlocomotion, vocalization, aversion to handling, and seizure susceptibility (E. Majchrowicz E, *Psychopharmacologia* **43**, 245-254, 1975). Chronic ethanol with repeated withdrawal in rats leads to a kindling-like condition with persistently heightened withdrawal severity (N. Kokka, D. W. Sapp, A.M. Taylor and R. W. Olsen, *Alcohol: Clin Exp Res* **17**, 525-531, 1993). This experimentally induced condition has been termed the chronic intermittent ethanol (CIE) model of drug dependence. In CIE animals, the hippocampus is in a state of hypoinhibition due to a decrease in the functional properties of GABA_A receptors (M. Kang, I. Spigelman, D. W. Sapp and R. W. Olsen, *Brain Res* **709**, 221-228, 1996). These observations suggest a connection between the effects of chronic intermittent ethanol, a reduced threshold to seizures induced by pentylenetetrazol (PTZ), and the inhibitory neurotransmitter GABA. In humans, alcohol dependency is due, in part, to alcohol-induced changes in the state of the brain that result in withdrawal signs and symptoms similar to those observed in CIE rats (REF). Therefore CIE in rats appears to be an appropriate model of alcohol dependency in humans. Consequently, compounds that reduce or prevent withdrawal signs in CIE rats would be expected to exert similar effects on withdrawal signs in humans with alcohol dependency. In the study on topiramate using CIE rats, the degree of ethanol-induced withdrawal was measured

quantitatively by the degree to which the threshold for PTZ-induced seizures was reduced. When topiramate was administered to CIE rats (40 mg/kg, i.p.) 1 hr prior to tail vein injection of PTZ, the threshold for seizures was significantly higher than for CIE rats treated with vehicle ($P < 0.05$) and was essentially the same as for control rats chronically treated with saline rather than ethanol (The R.W. Johnson Pharmaceutical Research Institute Document ID EDMS-USRA-2321301:3.0). Therefore, based on the threshold for PTZ-induced seizures as representative of ethanol withdrawal signs, topiramate essentially prevented this specific withdrawal sign in CIE rats.

For treating alcohol dependency, addiction and abuse, a compound of formula (I) may be employed at a daily dosage in the range of about 32 to 512 mg, usually in two divided doses, for an average adult human. A unit dose would contain about 16 to 128 mg of the active ingredient.

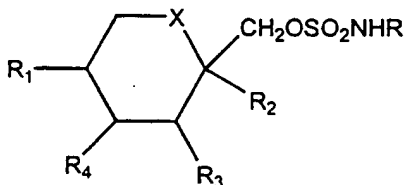
To prepare the pharmaceutical compositions of this invention, one or more sulfamate compounds of formula (I) are intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral, by suppository, or parenteral. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Thus, for liquid oral preparations, such as for example, suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like; for solid oral preparations such as, for example, powders, capsules and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques. Suppositories may be prepared, in which case cocoa butter could be used as the carrier. For parenterals, the carrier will usually comprise sterile water, though other ingredients, for example, for purposes such as aiding solubility or for preservation, may be included. Injectable solutions may also be prepared in which case appropriate stabilizing agents may be employed. Topiramate is currently available for oral administration in round tablets containing 25 mg, 100 mg or 200 mg

of active agent. The tablets contain the following inactive ingredients: lactose hydrous, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, synthetic iron oxide, and polysorbate 80.

The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder injection, teaspoonful, suppository and the like from about 25 to about 200 mg of the active ingredient.

WHAT IS CLAIMED IS:

1. A method for in treating alcohol dependency, addiction and abuse comprising administering to a mammal afflicted with such condition a therapeutically effective amount for treating such condition of a compound of the formula I:

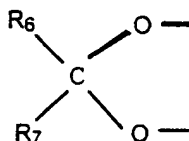


wherein

X is CH₂ or oxygen;

R₁ is hydrogen or alkyl; and

R₂, R₃, R₄ and R₅ are independently hydrogen or lower alkyl and, when X is CH₂, R₄ and R₅ may be alkene groups joined to form a benzene ring and, when X is oxygen, R₂ and R₃ and/or R₄ and R₅ together may be a methylenedioxy group of the following formula (II):



wherein

R₆ and R₇ are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

2. The method of claim 1 wherein the compound of formula I is topiramate.
3. The method of claim 1, wherein the therapeutically effective amount is of from about 32 to 512 mg.
4. The method of claim 1, wherein the amount is of from about 16 to 128 mg.